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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/041,958	01/07/2002	Saul Tzipori	21957	5351

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EXAMINER	
NAVARRO, ALBERT MARK	
ART UNIT	**PAPER NUMBER**
1645	12

DATE MAILED: 08/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/041,958	Tzipori et al
Examiner	**Art Unit**
Mark Navarro	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *26-36* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *26-36* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants amendment filed April 11, 2003 (Paper Number 10) has been received and entered. Consequently claims 26-36 remain pending in the instant application.

Claim Rejections - 35 USC § 112

1. The rejection of claims 34-36 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn.

2. The rejection of claim 31 under 35 U.S.C. 112, second paragraph, as being vague and indefinite in the recitation of "prevent neurological signs of HUS..." is withdrawn in view of Applicants amendment.

3. The rejection of claim 35 under 35 U.S.C. 112, second paragraph, as being vague and indefinite in the recitation of "at least about 0.5 micrograms/ml." is withdrawn in view of Applicants amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. The rejection of claims 26-36 under 35 U.S.C. 103(a) as being unpatentable over Krivan et al and Perera et al in view of Queen et al and Engelman et al is maintained.

Applicants are asserting that the prior art fails to teach any guidance as to (1) the selection of antibodies to Shiga toxin II only to treat or prevent HUS, or (2) what constitutes an effective dosage. Applicants assert that it would not have been obvious from studies using animals such as mice what an effective dosage would be, since mice are very resistant to infection, requiring many

times more toxin to become sick, than humans. Applicants conclude that only studies conducted in pigs or humans can be used to determine the critical components of the disease causing the etiological agent, what compounds would be effective to treat these critical components, and what the effective dosage of these compounds would be.

Additionally, Applicants have included multiple Declarations by Dr. Glunzer, Dr. Leong, and Dr. Tzipori.

Applicants arguments and Declarations have been fully considered but are not found to be fully persuasive.

First, Applicants assert that the prior art fails to teach any guidance as to (1) the selection of antibodies to Shiga toxin II only to treat or prevent HUS, and (2) what constitutes an effective dosage. However, Applicants are respectfully directed to the claims of Krivan *et al* (Patent No. 5,512,282). Claims 17-18 are directed to a method for the prevention and treatment of SLT toxemia (which left untreated can progress to Hemolytic Uremic Syndrome as set forth in column 1) **of a human** comprising administering monospecific polyclonal antibodies obtained by inoculating a bovine animal with a SLT selected from the group consisting of SLT I, SLT II, SLT IIV and mixtures thereof. The claim encompasses each of the toxins individually based upon the language of "selected from the group consisting of." Applicants are further directed to column 8, lines 49-52, which recites "A single type of SLT, such as SLT-II or a variant thereof, such as SLT-IIvp, can be injected." Applicants further assert that the prior art does not teach what

constitutes as an effective dosage. However, Applicants are directed to column 10, which sets forth that the usual dosage would be "100 mg to 5 gm of immunoglobulin." FDA approval, is not a prerequisite for finding a compound useful within the meaning of patent laws. (*Scott [v. Finney]*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 [(Fed. Cir. 1994)]. Office personnel should not require that an applicant demonstrate that a therapeutic agent based on a claimed invention is a safe or fully effective drug for humans. (*In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (CCPA 1977).

Second, Applicants have cited numerous Declarations. The Declaration of Dr. Glunzer sets forth that neonatal gnotobiotic colostrum deprived piglets have a unique potential as a model to evaluate prophylactic or therapeutic approaches offering new advantages to prevent or lessen systemic complications of EHEC infection in humans. However, this point is not germane to the rejection based upon the cited references. Krivan has disclosed methods of treatment and passive immunization with polyclonal antibodies to SLT II, the question is, is it obvious to use monoclonal antibodies in place of the disclosed monospecific polyclonals? Based upon the teachings of Queen *et al* (WO 90/07861) that humanized antibodies are substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin, there is sufficient motivation.

The Declaration by Dr. Leong addresses the same point. That neonatal gnotobiotic colostrum deprived piglets have a unique potential as a model to evaluate prophylactic or

therapeutic approaches offering new advantages to prevent or lessen systemic complications of EHEC infection in humans. However, this point is not germane to the rejection based upon the cited references.

The Declaration by Dr. Tzipori address several points. First, without studies in piglets it will take 10-12 years to determine the effective dose through Phase II/III clinical trials in humans. Second, Krivan *et al* describes the oral administration of polyclonal antibodies produced in cattle which are suitable for treating Stx-related disease in animals. Third, "Unquestionably, polyclonal antibodies made in animals, however purified, cannot be injected into the blood stream of humans, either for treatment or prevention." However, facts that should be considered in determining whether a specification is enabling, or if it would require an undue amount of experimentation to practice the invention include: the quantity of experimentation necessary to practice the invention. See In re Wands, 858 F.2d 731,737, 8 USPQ2d 1400, 1403 (Fed. Cir. 1988). While 10-12 years may seem like a substantial amount of time, it is deemed to be routine in that every drug to be administered to a human must pass through the identical Phase trials in order to receive FDA clearance. It simply does not rise to the level of excessive experimentation because the process take a substantial amount of time. Applicants further assert that Krivan *et al* describes the oral administration of polyclonal antibodies produced in cattle which are suitable for treating Stx-related disease in animals. However, this statement does not consider the complete teachings of Krivan *et al*. Applicants are directed to the claims which recite "comprising administering..."

(See claims 17-18). No limitation as to oral administration is recited. Applicants are further directed to column 11, lines 15-20, which sets forth that the preparations can be administered "intravenously, orally, intradermally, subcutaneously, intraoccularly, subconjunctively, intramuscularly and intathecally." It has long been held that a reference must be evaluated in its entirety, not on the basis of its preferred embodiments or working examples. In re Mills, 470 F.2d 649, 651, 176 USPQ 198 (CCPA 1972). Finally, Applicants Declaration asserts that "Unquestionably, polyclonal antibodies made in animals, however purified, cannot be injected into the blood stream of humans, either for treatment or prevention." However, attached for Applicants consideration is a CDC Drug Service showing Diphtheria Equine Antitoxin (intended for human use), which is a sterile, aqueous solution of the refined and concentrated proteins, chiefly globulins, containing antitoxic antibodies from the blood serum of horses that have been immunized against diphtheria toxin.

The claims are drawn to a dosage formulation comprising an effective amount of human or humanized monoclonal antibodies, the antibodies consisting of antibodies neutralizing Shiga like toxin II, to prevent or treat hemolytic uremic syndrome in a human.

Krivan et al (U.S. Patent Number 5,512,282) disclose of purified high titer, monospecific polyclonal antibodies to Shiga-like toxin obtained by a process of inoculating a bovine animal with a purified active SLT derived from *E. coli* and selected from the group consisting of SLT I, SLT

II, SLT IIV and mixtures thereof. Krivan et al further disclose of the passive immunization of a human or animal against SLT toxinemia comprising administering to the human or animal a prophylactically effective amount of the elicited antibody. (See claims 1 and 17). Krivan et al further disclose that SLT toxinemia can lead to hemolytic uremic syndrome. (See column 1). Krivan et al further disclose that "the present invention provides an antitoxin to **one** or more SLTs." (See column 6). Krivan et al further disclose that "A **single type of SLT, such as SLT-II** or a variant thereof, such as SLT-IIvp, can be injected. This provides polyclonal antibodies that are monospecific to just that type of SLT or variant." (See column 8).

Perera et al (Journal of Clinical Microbiology Vol 26, No. 10, pp 2127-2131, October 1988) teach of five monoclonal antibodies which bind to the α-subunit of SLT-II and were able to neutralize the toxin. (See abstract).

Neither Krivan et al nor Perera et al teach of monoclonal human or humanized antibodies.

Queen *et al* (WO90/07861) teach that methodology for the production of CDR-grafted antibodies having CDRs derived from the variable regions of non-human antibodies and framework regions derived from human antibodies were well established in the art at the time the claimed invention was made and that CDR-grafted antibodies were recognized to be useful reagents for diagnostic and therapeutic applications. Queen et al further set forth that humanized antibodies are substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin. (See abstract).

Engelman *et al* (Human Hybridomas and Monoclonal Antibodies. New York Plenum Press. 1985 pp 23-27) teach that methods for constructing human-human hybrids that secrete human monoclonal antibodies using lymphoblastoid cell lines as fusion partners were well known in the art at the time of applicants invention.

Given that 1) Krivan et al have disclosed of methods of passive immunization comprising administering high titer, monospecific polyclonal antibodies against Shiga-like toxin II, and that 2) Perera et al have demonstrated neutralization of SLT-II with monoclonal antibodies which specifically bind the α-subunit of SLT-II, and that 3) Queen et al has taught of the advantages of humanized antibodies over non-human antibodies for therapy in humans, and that 4) Engelman et al has also taught of the advantages of human monoclonal antibodies over non-human monoclonal antibodies for therapy in humans, it would have been prima facie obvious to one of ordinary skill in the art to have generated a humanized antibody or a human monoclonal antibody as taught by Queen et al and Engelman et al, for use in the method disclosed by Krivan et al. One would have been motivated to produce such an antibody based on the advantages described by Queen et al and Engelman et al, (i.e., substantially decreased immunogenicity). One would have been further motivated to humanize an antibody which binds the α-subunit of SLT, based on the demonstration of neutralization as shown by Perera et al.

It is noted that the references do not teach the amount of antibodies set forth in claims 34 or 36. However, determining the precise dosage of a humanized antibody is merely the result of

optimizing a result effective variable. As set forth In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219, (CCPA 1980), it is normally within the skill in the art to optimize a result effective variable.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Navarro, whose telephone number is (703) 306-3225. The examiner can be reached on Monday - Thursday from 8:00 AM - 6:00 PM. The examiner can be reached on alternate Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Lynette Smith can be reached at (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1645 by facsimile transmission. Papers should by faxed to Group 1645 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703) 308-4242.

Mark Navarro

Primary Examiner

August 8, 2003